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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/828,330	04/06/2001	Wayne P. Franco	388450.0002	5651

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EXAMINER	
NICHOLS, CHRISTOPHER J	
ART UNIT	**PAPER NUMBER**
1647	15

DATE MAILED: 06/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/828,330	FRANCO, WAYNE P.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-43 and 47* is/are pending in the application.

4a) Of the above claim(s) *25-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-24,35-43 and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 April 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

1. The "Request for Clarification and/or Vacation of Office Action and Issuance of a New Office Action" filed 30 May 2003 (Paper No. 17) has been received and taken into consideration. The Applicant is correct in that claims 35-43 which were rejected in Office Action (Paper No. 11, 18 September 2002) but were not included in the last Office Action mailed 20 March 2003 (Paper No. 16). The exclusion of claims 35-43 from the last Office Action (Paper No. 16, 20 March 2003) was inadvertent and the Examiner regrets the error.

2. The previous Office Action (Paper No. 16) mailed 20 March 2003 is hereby VACATED.

3. The instant Office Action hereby replaces the vacated Office Action with ALL pending claims included.

4. The Amendments filed 27 January 2003 (Paper No. 12, 13, 14, and 15) have been entered in full. Claims 44-46 and 48-53 have been cancelled. Claims 25-34 remain withdrawn from consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected material, there being no allowable generic or linking claim. Claims 16-24, 35-43, and 47 are under examination.

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

6. The objection to the specification as set forth at pp. 2-3 ¶ 4-9 of the previous Office Action (Paper No. 11, 18 September 2002) is *withdrawn* in view of Applicant's amendments (Paper No. 15, 27 January 2003).

7. The objection to the claims as set forth at pp. 4 ¶10 of the previous Office Action (Paper No. 11, 18 September 2002) is *withdrawn* in view of Applicant's amendments (Paper No. 15, 27 January 2003).

8. The instant Application is now in compliance with Sequence Rules as set forth at pp. 4 ¶11 of the previous Office Action (Paper No. 11, 18 September 2002) due to Applicant's amendments (Paper No. 15, 27 January 2003).

9. The rejection of claims 44-46 and 48-53 as set forth at pp 6-9 ¶13-15 of the previous Office Action (Paper No. 11, 18 September 2002) is *moot* due to Applicant's amendment (Paper No. 15, 27 January 2003) canceling claims 44-46 and 48-53.

Maintained Objections And/Or Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims **16-24, 35-43,** and **47** are rejected under 35 U.S.C. 112 ¶1 as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the

invention for the reasons as set forth in at pp. 4-6 ¶12 of the previous Office Action (Paper No. 11, 18 September 2002).

11. The Applicant traverses the 35 USC 112 ¶1 rejection of claims 16-24, 35-43, and 47 as set forth in at pp. 4-6 ¶12 of the previous Office Action (Paper No. 11, 18 September 2002) on the grounds that those skilled in the art would be able to practice the invention in light of the specification and prior art (pp. 8-13 Rejections under 35 U.S.C. § 112 ¶1, Paper No. 15). Applicant's arguments have been fully considered but are not deemed to be persuasive for the following reasons.

12. The Applicant discusses US 5915378, US 5254330, US 4409237, US 6436902, and Paper No. 14 Declaration of Wayne P. Franco, M.D. Under 37 C.F.R. § 1.132 (27 January 2003) ¶11-12 as examples of formulation of therapeutically active drug species for pulmonary delivery, crystalline sugar carriers for dry powder formulations that are amenable for use with a wide variety of pharmacological agents, lyophilic carrier compositions, and the potential use of growth factors in a dry powder form (pp. 9-10). The Examiner *accepts* this argument that FGF-1, FGF-2, and/or VEGF could be prepared in such a manner and administered via inhalation.

13. While the Declaration indicates that growth factors can be administered via inhalation, there is no evidence that such would be effective for treatment of coronary artery disease, as required by the claims. Due to the large quantity of experimentation necessary to test all the invention, the lack of direction/guidance presented in the specification regarding evaluating results of the therapy, the absence of working examples directed to inhaling protein growth factors, the complex nature of the invention, the unpredictability of the effects of growth factors on humans [Kutryk and Stewart (1 February 2003) "Angiogenesis of the Heart." Microscopy

Research and Technique **60**(2): 138-58] and the breadth of the claims which fail to recite limitations for what effects inhaling protein growth factors would have on a patient, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

14. The Applicant traverses the rejection under 35 USC 112 ¶1 on the grounds that claims 16-24, 35-43, and 47 that the specification and prior art offers enough guidance such that a person of ordinary skill in the art would be confident that FGF-1, FGF-2, and VEGF would reach the target organ, in this instinct case, the heart, via the circulatory system by way of pulmonary administration (pp. 10-11). The Applicant cites US 5915378, US 5006343, and Paper No. 14 Declaration of Wayne P. Franco, M.D. Under 37 C.F.R. § 1.132 (27 January 2003) ¶6-7. The Examiner *accepts* this argument that FGF-1, FGF-2, and/or VEGF would reach the heart via the circulatory system after pulmonary administration. However, the Examiner maintains the rejection under 35 USC 112 ¶1 for claims 16-24, 35-43, and 47 on the grounds that the desired effect would not be achieved via the claimed method. Instead, all tissues exposed to FGF-1, FGF-2, and VEGF would undergo cell division and angiogenesis in addition to a mucosal irritation of the pulmonary passages.

15. US 4296100 specifically states that FGF is biologically active at low dosages such as 1 to 10 nanograms or 25 to 200 nanograms wherein is exerts a mitogenic effect on mammalian endothelial cells (Col. 2 lines 30-41). This would include the mucosal lining of the mouth and sinuses, pulmonary passages, and the circulatory system.

16. The Applicant discloses that some experimentation is required to practice the invention in regards to therapeutic agents which might be used in an embodiment of the instant invention (pp. 11).

17. The Examiner agrees and adds that the art teaches that growth factors including FGF and VEGF have been used in clinical trials to treat cardiovascular disease with varying degrees of success. Freedman and Isner [(March 2001) "Therapeutic Angiogenesis for Ischemic Cardiovascular Disease." J Mol Cell Cardiol **33**(3): 379-93] teach that clinical studies evaluation the form (DNA versus protein), the route of administration, dosage, formulation, and combinationof growth factors in treating cardiovascular diseases is required (Abstract). Freedman and Isner teach that recombinant FGF and/or VEGF administered systemically, such as by inhalation, can lead to potential adverse side effects such as hypotension and edema with VEGF and anemia, thrombocytopenia and renal toxicity with FGF (pp. 381-382; pp. 386-387). Further Freedman and Isner caution that the broad spectrum mitogenic effects of FGF and VEGF may trigger occult neoplasms (pp. 386).

18. The Examiner furthers the statement in that the art teaches that growth factors including FGF-1 and VEGF affect a wide range of cell types (Slavin 1995; Jin *et al.* 2002). Regarding use of growth factors, the art recognizes that growth factors can have complementary and/or competitive physiological effects.

19. Also, the growth factor cited in claim 20 themselves are members of large families with individual variants and isoforms. For instance, Merck & Co. Inc. (GB 2 332 373 A) teaches that vascular endothelial growth factor (VEGF) has isoforms such as VEGF-A (mature isoforms containing 206, 189, 165, 145, and 121 amino acid residues), VEGF-B, VEGF-C, and VEGF-D.

20. Due to the large quantity of experimentation necessary to test all the applicable ratios growth factors, the lack of direction/guidance presented in the specification regarding evaluating growth factor effects on animal models, the absence of working examples directed to all growth factors, the complex nature of the invention, the unpredictability of the effects of growth factors on animals, including humans [Simons *et al.* (12 September 2000) "Clinical Trials in Coronary Angiogenesis: Issues, Problems, Consensus." Circulation **102**: e73-e86; Jośko *et al.* (2000) "Vascular endothelial growth factor (VEGF) and its effect on angiogenesis." Med. Sci. Mont. **6**(5): 1047-1052] and the breadth of the claims which fail to recite limitations for what effects any given growth factor would have on a patient, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

21. The Applicant puts forth the proposition that VEGF activity is stimulated in oxygen-free environments. In addition, a clinician can take the precaution of having a patient immediately rinse their mouth area after inhalation with water. Finally, that direct inhalation is a more direct route for the administration of growth factors than intravenous administration (pp. 11-13). The Applicant cites Jöspin et al. and Paper No. 14 Declaration of Wayne P. Franco, M.D. Under 37 C.F.R. § 1.132 (27 January 2003) as support.

22. Concerning the action of VEGF in anoxia conditions only, Jośko *et al.* [(2000) "Vascular endothelial growth factor (VEGF) and its effect on angiogenesis." Med. Sci. Mont. **6**(5): 1047-1052] teaches that hypoxia activates secretion of VEGF and upregulates VEGF receptor expression (pp. 1048-1049). In addition, Jośko et al. demonstrates that VEGF is active in aerobic conditions *in vitro* and *in vivo*. Furthermore, Jin *et al.* [(2002) "Vascular endothelial growth factor (VEGF) stimulates neurogenesis in vitro and in vivo." PNAS Early Edition pp. 1-5]

teaches the VEGF has cell specificity not only to endothelial cells (a large group of cells), but stimulates neuronal growth *in vitro* and *in vivo* (pp.1). Further, VEGF stimulated cell growth in cultured cortical cells and in rat brains (Fig. 1-4). Also, the *in vivo* work demonstrated that VEGF exerting its mitogenic effect on astrocytes and neurons as well as endothelial cells (Fig. 6). All of Jin et al.'s work was done in aerobic conditions (**Materials and Methods** pp. 1-2). Therefore, it is not clear whether or not VEGF would have the claimed specific targeting to the desired organ, in this instant case, the heart, or if VEGF would be preferentially active in only anaerobic conditions as described the Declaration. Thus the assertion that VEGF is activity is heavily dependent upon hypoxic conditions is contrary to the prior art [Paper No. 14 Declaration of Wayne P. Franco, M.D. Under 37 C.F.R. § 1.132 (27 January 2003) ¶14-15].

23. Furthermore, any inhaled growth factor would certainly not fail to reach the brain of the patient. Bikfalvi *et al.* (1997) ["Biological Roles of Fibroblast Growth Factor-2." Endocrine Reviews **18**(1): 26-45] teaches that FGF-2 varies in its effects on glia, astrocytes and oligodendrocytes. For instance, while FGF-2 can induce dedifferentiation and proliferation of oligodendrocytes, these glia remain committed to the oligodendrocytic linage (pp. 34). On the other hand, Bikfalvi et al. (1997) teaches that FGF-2 will only induce proliferation in astrocytes (pp. 34). A person of ordinary skill in the art would not have evidence or prior art to guide them as to avoid these unintended consequences of inhaling FGF-2.

24. Concerning rinsing the patient's mouth area with water following administration of VEGF, FGF-1, FGF-2, or mixtures thereof [Paper No. 14 Declaration of Wayne P. Franco, M.D. Under 37 C.F.R. § 1.132 (27 January 2003) ¶16]. The Examiner holds this to be ineffective as the growth factors will be quickly absorbed and any such post-administration rinses is

inadequate. However, absent working examples of this point it is not clear whether or not this approach is effective. As for delivery to the left atrium and ventricle of the patient's heart, this is accepted. Yet, the growth factors will not only be delivered to the left side of the heart but throughout the patient's body.

25. In regards to circulation directly delivering the growth factors to the heart, Freedman and Isner [(March 2001) "Therapeutic Angiogenesis for Ischemic Cardiovascular Disease." J Mol Cell Cardiol **33**(3): 379-93] teach that the effects of ciruclation on delivery of a growth factor such as FGF and VEGF can not be discounted as complicating factors (pp. 383). Also, Jośko et al teaches that VEGF acts as a paracrine factor, affecting all endothelial cells within the range of distribution (pp. 1050).

26. Therefore, the rejection of claims 16-24, 35-43, and 47 under 35 USC 112 ¶1 is maintained.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

27. Claim **47** recites the limitation "claim 44" in the first line. There is insufficient antecedent basis for this limitation in the claim. Claim 44 has been canceled and therefore cannot be the parent claim of a dependent claim.

Summary

29. It is noted that the US patents and Jösko et al. reference cited by the Applicant in Paper No. 15 (27 January 2003) have been made of official record in the instant PTO-892 form.

30. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Gary L. Kunz

GARY KUNZ
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

CJN
June 4, 2003

Gary L. Kunz
GARY KUNZ
SUPERVISORY PATENT EXAMINER
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